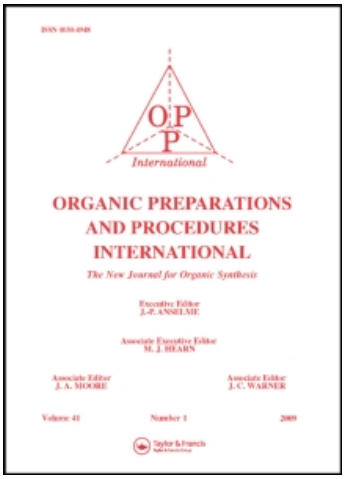

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AN IMPROVED SYNTHESIS OF 9-CHLORO-1,8-*p*-MENTHADIENE

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AN IMPROVED SYNTHESIS OF 9-CHLORO-1,8-*p* -MENTHADIENE†

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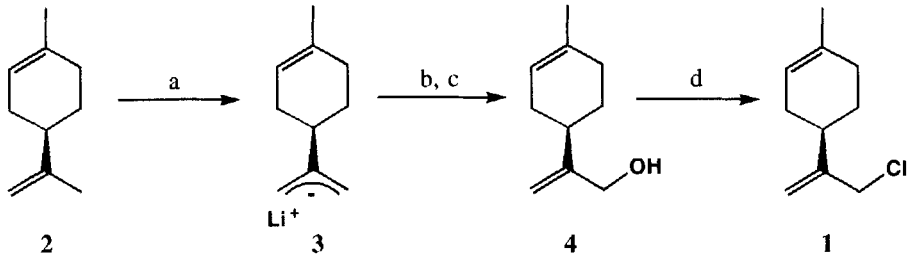
During a recent study, 4R-(+)-9-chloro-1,8-*p*-menthadiene (**1**) was required. A review of the literature indicated that this allylic chloride had been previously described as a side-product of the

reaction of 4R-(+)-limonene (**2**) with *t*-butyl hypochlorite;[1] however, the yield (10 %) and specific optical rotation (+ 23.6° in chloroform) reported precluded the use of this procedure for our synthesis. Compound **1** was also employed by Sakai *et al.*,[2] but no experimental details regarding its synthesis and physical properties were included in this work.



a) *n*-butyllithium, TMEDA, room temperature, 24 hrs; b) O_2, -35°;
c) Na_2SO_3, 36% overall; d) PPh_3, CCl_4, CH_2Cl_2, reflux, 91%

Herein, we describe a simple reaction sequence which affords gram quantities of **1** with higher yields and better optical purity than previously reported.

In our approach outlined above, the intermediate anion **3**, obtained by chemoselective metalation of 4R-(+)-limonene (**2**) with the *n*-butyllithium-N,N,N',N'-tetramethylethylenediamine (TMEDA) complex,[3] was quenched with oxygen at low temperature to give the alcohol **4** in 36% overall yield after a reductive work up and a fractional distillation that allowed the partial recovery of TMEDA and the unreacted limonene. Finally, treatment of **4** with the triphenylphosphine-carbon tetrachloride couple in refluxing methylene chloride afforded **1** in 89-91% yield after a non-aqueous work-up. Similarly, 4S-(-)-**1** was obtained from 4S-(-)-**2** in 32% overall yield.

In this sequence of reactions, there was no noticeable racemization of either enantiomer of **4** and **1** based on several experiments and supported by previous reports.[3,4] The first step of this sequence was orginally developed by Crawford *et al.*,[3] where no racemization was claimed. In an addition to this evidence, we did the comparative ^1H NMR studies of the both enantiomers of compound **4** with their Mosher esters and the diasteromers obtained by adding the chiral $Eu(hfc)_3$ shift reagent. In both the cases, we did not observe any further multiplicity of the corresponding peaks from the original spectrum, hereby, supporting Crawford's claim. Beside this, we also studied the GC of Mosher esters of the compound **4** and found one single peak in each case which indirectly provided additional support for the 100% optical purity of the reaction product **4**. In a similar fashion, we determined the enantioselectivity of the second step by the GC experiments and found that the allylic halide **1** was greater than 98% optically pure which was further supported by the earlier report.[4]

EXPERIMENTAL SECTION

All the experiments were performed under a dry nitrogen atmosphere. 4R-(+)-limonene was used as received from Aldrich Chemical Co., TMEDA was distilled from potassium hydroxide, carbon tetra-

chloride and methylene chloride were used freshly distilled from phosphorus pentoxide and triphenylphosphine was melted under vacuum prior to use. The ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75.4 MHz, respectively on a Varian VXR 300 instrument in deuteriochloroform, using TMS as internal standard. IR spectra were obtained with a Perkin Elmer 281B spectrophotometer, while the optical rotations observed at the Na-D line were determined at 25° with a Perkin Elmer 141 polarimeter. The mass spectrum at 70 eV was determined with a Finnigan 3221-F200 mass spectrometer. A Hewlett Packard 5890 gas chromatograph, with a 15 m DB-1 column, in the isothermic mode (160°) using helium (1 mL/min) as carrier, was employed for purity analysis. The elemental analysis was performed by Atlantic Microlab, Norcross, GA.

1,8-*p*-Menthadien-9-ol (4).- To a stirred solution of the *n*-butyllithium-TMEDA complex, prepared from 138 mL (309 mmol) of *n*-butyllithium in hexane and 46.5 mL (309 mmol) of TMEDA, was added 100 mL (618 mmol) of 4R-(+)-limonene (**2**) in 10 min. The resulting solution, which acquired a deep red color in 30 min, was stirred at room temperature for 24 hrs. After cooling to -35°, a slow stream of oxygen was bubbled through the solution until decolorization occurred. The resulting hydroperoxides were reduced with 280 mL of a 25% sodium sulfite solution over 2 hrs at room temperature. The organic phase was removed, and the aqueous phase was extracted with 3 x 200 mL of ether. The combined organic phases were dried, and the ether was evaporated at room temperature *in vacuo*. TMEDA was recovered by distillation at 60°/ 50 mm Hg, then the unreacted limonene was separated at 60° /5 mm Hg and finally 17.03 g (36 %) of **4** were recovered as a colorless oil, bp. 104°/ 1 mm Hg. $[\alpha]_D^{25}$: +106° (c = 0.38, EtOH), lit.[3] +104° (c = 0.33, EtOH).

IR (thin film): 3320, 2980-2810, 1640, 1430, 1050, 1020, 900, 800 cm^{-1}; ^{1}H NMR: δ 5.36 (bs, 1H), 5.00 (bs, 1H), 4.83 (bs, 1H), 4.06 (s, 2H), 3.33 (bs, 1H), 2.36-1.40 (m, 7H), 1.63 (s, 3H).

9-Chloro-1,8-*p*-menthadiene (1).- A solution of 4.42 g (29.mmol) of **4** in 10 mL of carbon tetrachloride was added to a stirred solution of 8.48 g (32.3 mmol) of triphenylphosphine in 10 mL of methylene chloride and the mixture was refluxed for 3 hrs. After removal of the solvent under reduced pressure, the remaining solid was shaken up in 3 x 70 mL of hexane and the suspended triphenylphosphine oxide was separated by filtration; the hexane solution was concentrated *in vacuo*, affording an oil which was distilled to give 4.51 g (91%) of **1**, as a colorless oil, bp. 108° / 0.25 mm Hg, $[\alpha]_D^{25}$: +84.8° (c = 0.21, $CHCl_3$).

IR (thin film): 3080-2800, 1635, 1440, 1375, 1255, 1150, 910, 800, 750, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.42 (bs, 1H), 5.16 (s, 1 H), 5.00 (s, 1 H), 4.10 (s, 2H), 2.46-1.40 (m, 7H), 1.66 (s, 3H) (chemical shifts are in agreement with those reported by Ravindranath and Srinivas[1]); ^{13}C NMR ($CDCl_3$): δ 149.6, 133.8, 120.2, 113.1, 47.8, 36.5, 31.2, 30.4, 28.0, 23.4; MS, m/e (%): 172 (M^+, 1), 170 (M^+, 3), 135 (11), 134(16), 121(26), 119(13), 107(13), 105(19), 95(14), 94(14), 93(63), 92(17), 91(51), 81(17), 79(53), 77(35), 68(100), 67(93), 55(23), 53(25).

Anal. Calcd for $C_{10}H_{15}Cl$: C, 70.37; H, 8.86; Cl, 20.77. Found: C, 70.24; H, 8.83; Cl, 20.86

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5-NITRO-2-FURYL DIIMIDOYL DISULFIDES BY IODINE OXIDATION OF *N*-ARYL-5-NITRO-2-THIOFURAMIDES†

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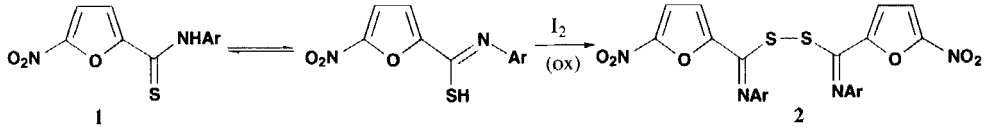
One of the most striking differences between of thioamides and amides is their behavior on oxidation. While amides are oxidized at the carbon atom of the side-chain under forcing conditions, their thio analogues are readily attacked at the sulfur atom yielding a variety of products. The type of product is highly dependent on the oxidizing agent used; desulfurization and the formation of disulfides, sulfides, thioamide *S*-oxides, heterocycles have been observed.[1] The most favorable method for conversion to diimidoyl disulfides seems to be the oxidation by iodine.[2]



a) Ar = C_6H_5; b) Ar = *o*-MeC_6H_4; c) Ar = *m*-MeC_6H_4; d) Ar = *p*-MeC_6H_4;
e) Ar = *p*-$MeOC_6H_4$; f) Ar = *p*-ClC_6H_4; g) Ar = *p*-$NO_2C_6H_4$.